Transplantation of the Heart in an Infant and an Adult*

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STUDIES OF orthotopic allotransplantation of canine hearts, initiated in this institution in 1963, have been continued to the present.[1-6] The purpose of these studies was to develop a treatment for lethal cardiac lesions not amenable to medical or surgical correction. These included certain congenital defects and acquired lesions, such as severe myocardial damage secondary to cardiomyopathies, arteriosclerosis, or multiple valvar disease. By the spring of 1966 the experimental results were considered sufficiently encouraging to warrant clinical application.

On May 11, 1966, a cyanotic male infant was delivered at the Maimonides Medical Center. The findings at physical examination, catheterization, and angiography were consistent with the diagnosis of pulmonary atresia with patent ductus arteriosus, ventricular and atrial septal defects, and corrected transposition. Inasmuch as surgical treatment was not possible, the infant was considered a potential recipient for a cardiac allograft.

A male anencephalic born on June 27, 1966, was considered a possible donor and so was transferred to Maimonides Medical Center on June 28. There were no other gross abnormalities. Spontaneous and reflex motor activity ceased, and mechanical ventilation became necessary to sustain myocardial contractions. The anencephalic infant's heart ceased beating at 12:21 A.M. on June 30. Attempts to perfuse and resuscitate this heart, however, were unsuccessful and the operation was abandoned. Despite the fact that transplantation was not accomplished in this instance, the experience served as a trial of our criteria for selection of both donor and recipient and suggested the realistic possibility of using anencephalic infants as the source of the donor organ.

CASE REPORTS

CASE 1. The next patient for whom heart transplantation was considered was born on November 18, 1967. This 2,600 gm. cyanotic white baby was delivered at this center after an uneventful gestation by a 37 year old secundigravida. The infant was in moderate respiratory distress with a respiratory rate of 80/min. and a heart rate of 180/min. Cyanosis was generalized and evenly distributed. The femoral and brachial pulses were normal in timing and intensity. There was no venous distention, abnormal arterial pulsation, precordial bulge, parasternal heave, apical lift, or thrill. The maximal impulse was diffuse in the area of the fourth left intercostal space 1 cm. to the right of the nipple line. The first heart sound was of normal intensity and maximal at the fourth left intercostal space in the nipple line. The second heart sound was single and decreased at the base. No third heart sound was discernible. No murmur, click, or friction rub was present.

The chest roentgenogram revealed a cardiothoracic ratio of 60 per cent and decreased pulmonary vascular markings. The electrocardiogram (Fig. 1) revealed a frontal QRS axis of +100°. The P waves were tall and spiking, measuring 4 to 5 mm. in lead II. An rSR' pattern was present in the right precordial leads.

Cardiac catheterization and cineangiocardiography (Fig. 2) were performed on November 20. The catheter could not be passed into the right ventricle. A large right to left atrial shunt was demonstrated by oximetric studies. Angiography revealed huge right to left shunting at the atrial level. The left side of the heart appeared normal. The right ventricle and pulmonary artery were not

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visualized. The pulmonary vasculature filled poorly, presumably by way of the bronchial vessels. There was good filling of the aorta, with no visualization of a ductus arteriosus. The diagnosis was tricuspid atresia (type IA of Keith et al.[7]) with atrial communication.

A palliative intrapericardial aorticopulmonary shunt was created through the right lateral fourth interspace on November 20. A 4 mm. anastomosis was constructed with the use of 6-0 Tevdek®. Postoperatively, oxygen saturation rose from 45 to 80 per cent. Nonetheless, the infant had frequent episodes of apnea which required endotracheal intubation and assisted ventilation. Pulmonary edema and congestive failure were treated with morphine sulfate, chlorpromazine, diuretics and digitalis. By the fourth postoperative day the infant's condition appeared somewhat improved. However, he did not respond well to stimulation, did not suck well and remained at his birth weight. The heart rate was 170 beats/min., and the respiratory rate 70/min. Cyanosis was milder, but the liver edge was palpable 4 to 5 cm. below the right costal margin. Chest roentgenogram revealed findings consistent with progressive, refractory congestive cardiac failure. We believed that there was so little chance that the baby could survive another palliative operation that definitive cure by transplant was a therapeutic possibility.

On December 4 an anencephalic infant was transferred here. This grossly malformed infant required endotracheal intubation with assisted ventilation to sustain its myocardial contractions (Fig. 3). However, evaluation of the heart by physical examination, electrocardiogram and chest roentgenogram disclosed no abnormality. Catheterization was not feasible because of the infant's poor general condition. Both donor and recipient were blood type A, Rh positive, and determination of lymphocyte histocompatibility by means of the irradiated hamster test disclosed no evidence of major incompatibility.

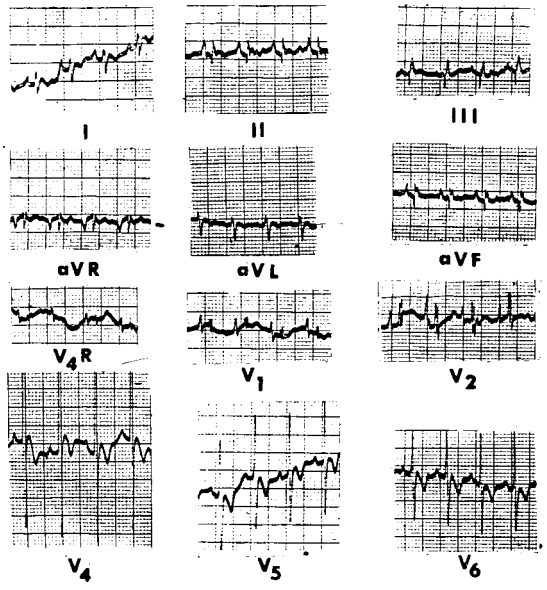

Figure 1. Case 1. *Electrocardiogram.*

Operation: During the early morning hours of December 6, 1967, the donor's cardiac rhythm became irregular, and both infants were brought to the operating room. At 3:45 A.M. external cooling by immersion in ice water was begun (Fig. 4) in both infants. The donor infant was heparinized (3.5 mg./kg.). At 4:25 A.M. spontaneous cardiac activity ceased in the donor infant; his body temperature was then 27° C. The chest was immediately opened through the fourth interspace bilaterally, and the heart was excised and immersed in normal saline solution at approximately 5° C. No gross abnormalities were evident. The donor heart was excised close to the cavae and pulmonary veins so that the atrial appendages were included in the graft, as were long segments of the pulmonary artery and aorta.

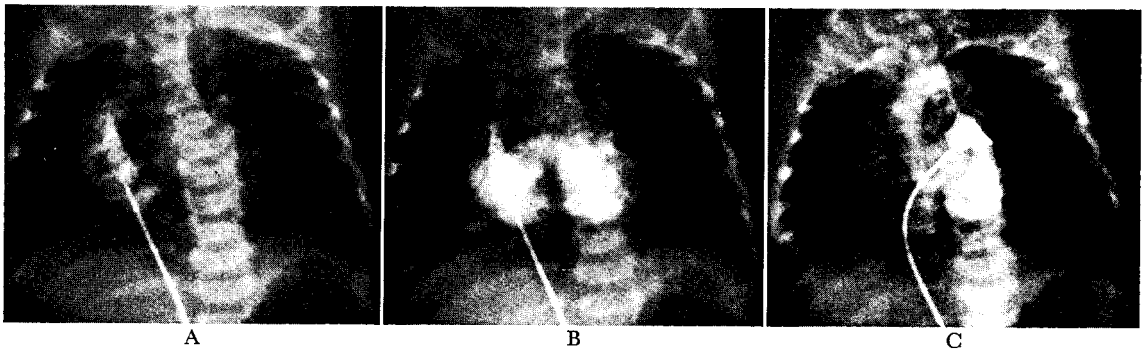

Figure 2. Case 1. *Angiocardiograms.* **A,** filling of right atrium. **B,** right atrial injection, filling right atrium, left atrium, and left ventricle. There is no filling of the right ventricle. **C,** left atrial injection showing filling of left atrium, left ventricle, and aorta. No patent ductus arteriosus is seen, and there is no left to right shunting at atrial or ventricular level.

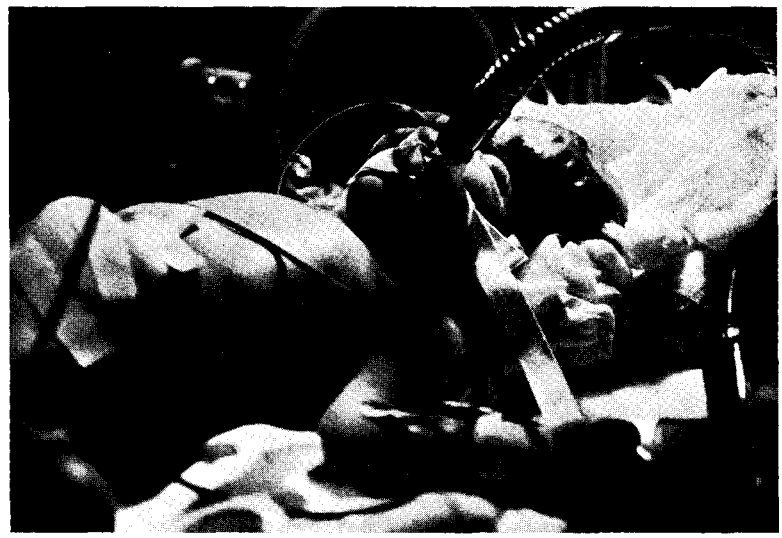

Figure 3. Case 1. *Donor infant.*

At 4:25 A.M. a second surgical team in an adjacent room began to perform a bilateral anterior thoracotomy on the recipient through the fourth interspaces. Venticular fibrillation occurred as the chest was being opened, and manual systole was carried out until 4:45 A.M., when it was apparent that the donor heart was normal. The body temperature of the recipient was 17° C. Cooling was stopped at this time.

In preparation for removal of the malformed recipient heart, occlusive tapes were placed about the superior and inferior venae cavae. A vascular clamp was placed through the transverse sinus as far distal as possible, and the heart was excised, leaving a generous cuff of the atrial walls and long stumps of the pulmonary artery and aorta.

Beginning with the left atrium, the donor heart was sutured in place by a continuous over-and-over suture (Fig. 6). The interatrial septum was sutured next, followed by the right atrium, aorta and pulmonary artery. Care was taken to flush air from both sides of the heart with buffered electrolyte solution instilled through catheters placed through pursestring sutures in the atria. The anastomoses were completed by 5:20 A.M. and manual systole was reinstituted.

Rewarming was begun with saline warmed to 40° C. in the tub and by pouring warm saline into the chest cavity. Spontaneous sinus rhythm resumed at 5:30 A.M. at a body temperature of 23° C. Ven-

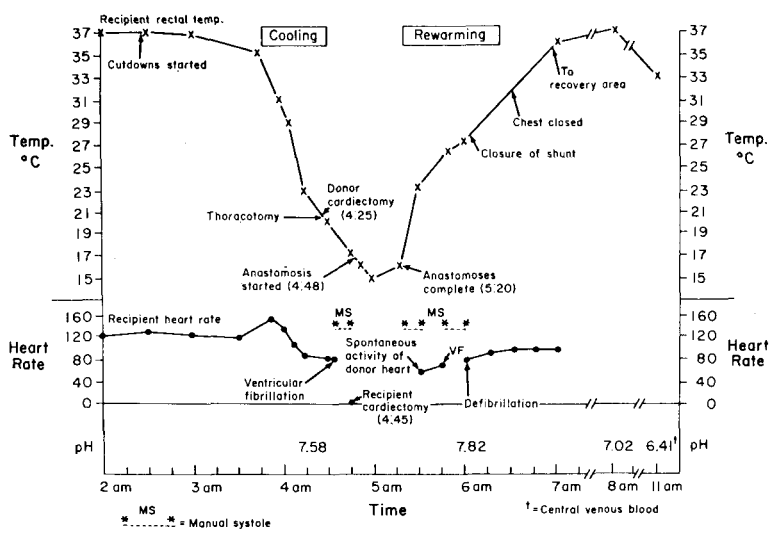

Figure 4. Case 1. *Sequence of events* and physiologic parameters during operation.

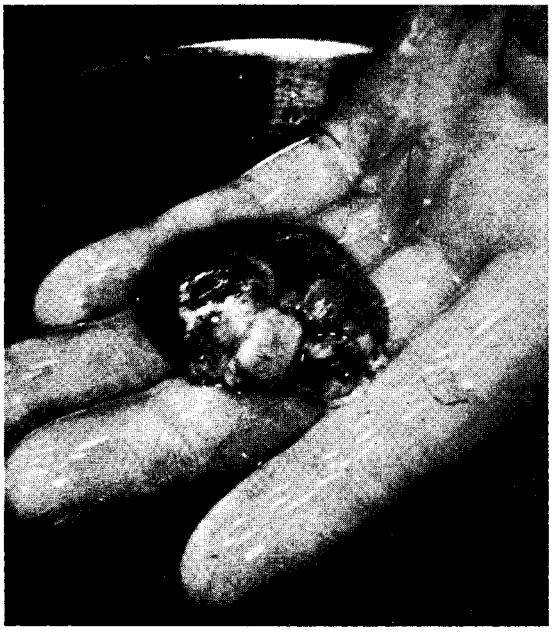

Figure 5. Case 1. *Cardiac allograft* used in this case.

tricular fibrillation occurred and responded to a single direct current countershock at 26° C. Isoproterenol was given slowly by intravenous drip.

Attempts were then made to close the previously created intrapericardial aorticopulmonary anastomosis. The chest was closed in layers with bilateral underwater chest tube drainage and the infant was moved to an isolation area at 7:00 A.M. At this time the infant's temperature was 36°C., and the heart rate ranged from 90 to 110 beats/min. Since the baby's spontaneous respiratory efforts were considered inadequate, an endotracheal tube was left in place and ventilation was assisted.

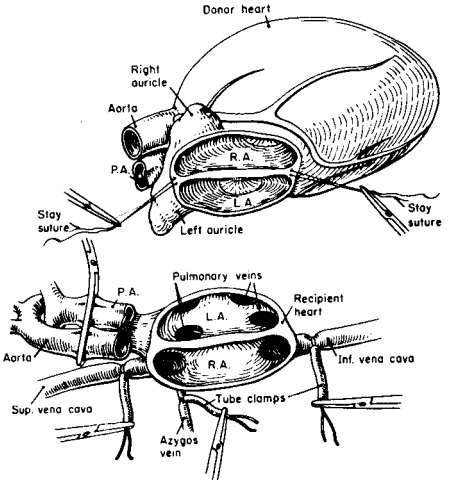

Figure 6. Case 1. *Preparation* of recipient's atrial stump and of graft.

Postoperative Course: The infant moved all limbs spontaneously and appeared to be responding satisfactorily for the first several hours. However, metabolic and respiratory acidosis developed rapidly, and his temperature fell to 33° C. Despite correction of the metabolic acidosis with bicarbonate and attempted correction of the respiratory acidosis with hyperventilation, bradycardia and cardiac arrest occurred at 12:15 P.M. Resuscitative efforts with sternal compression and, later, open chest manual systole, followed by direct intracardiac injection of cardiotonic drugs, all failed.

Autopsy showed diffuse atelectasis of both lungs. The transplanted heart appeared normal. The suture lines were intact; there were no intracardiac thrombi or signs of leakage from the heart. The aorticopulmonary anastomosis was reduced in caliber but still patent, and there was slight narrowing of the right main pulmonary artery.

The recipient's malformed original heart (Fig. 7) weighed 19.5 gm. without the posterior atrial walls. The right atrium was markedly enlarged and its wall greatly thickened. The tricuspid valve was severely deformed, leaving a widely patent atrioventricular orifice. The leaflets of the tricuspid valve were displaced to the base of the right ventricle, where they were fused with their rudimentary chordae tendineae to cause almost complete membranous obstruction to the outflow tract of the right ventricle below the infundibulum. The right ventricular cavity was rudimentary. In addition, there was a large atrial septal defect. The final anatomic diagnosis was severe Ebstein's malformation of the tricuspid valve with subvalvular right ventricular outflow tract obstruction.

CASE 2. A second transplantation was performed early in January 1968. A 57 year old white man with a nine year history of progressive cardiac disability was admitted to the Maimonides Medical Center on December 10, 1967. This condition had been initiated by a myocardial infarction complicated by pericardial and pleural effusion. Recurrences of these complications necessitated 14 hospital admissions over the intervening years. Diabetes mellitus was detected in 1963. In 1964 the patient suffered a right hemiplegia with dysphasia, from which he completely recovered. Progressive decrease in effort tolerance forced his retirement as a fireman and finally as a shopkeeper. Medical support had included the use of digoxin, furosemide, hydrochlorothiazide, spironolactone, warfarin and tolbutamide. However, during the 18 months prior to admission the patient's condition had progressively deteriorated until dyspnea occurred at rest, sleep was possible only when sitting up and effort beyond taking 10 steps was intolerable.

On examination the cardiac rhythm was regular, the heart rate 70 beats/min. and the blood pressure 100/65 mm. Hg. The central venous pressure was

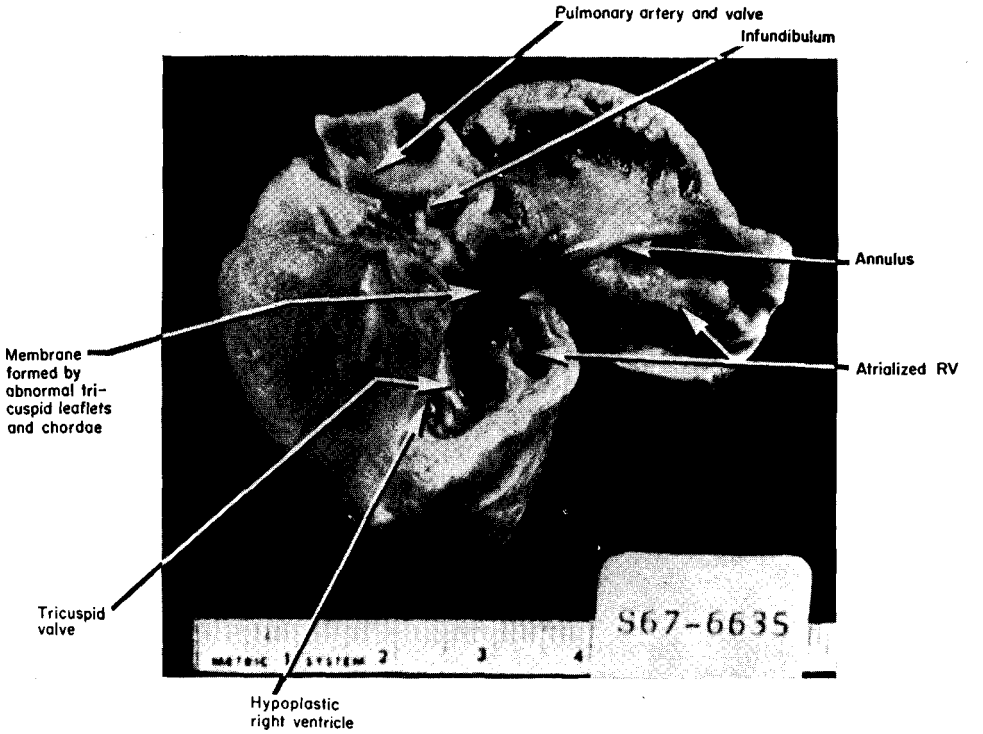

Figure 7. Case 1. *Recipient's excised heart.*

elevated to 18 cm. H_2O. The cardiac apex was palpated in the fifth left intercostal space in the anterior axillary line and was left ventricular in character. The first heart sound was decreased in intensity; there was paradoxic splitting of the second sound with increased intensity of the pulmonic component. A grade 2/6 pansystolic murmur was maximal at the apex and radiated into the axilla. Bilateral basilar crepitations were present in the lungs and the liver was enlarged to 4 cm. below the costal margin and was tender. There was no peripheral edema or ascites.

The electrocardiogram (Fig. 8) showed an intraventricular conduction defect (QRS = 0.16 sec.) as well as prolonged A-V conduction (P-R interval = 0.24 sec.). The changes were considered consistent with extensive anterolateral wall infarction of the myocardium although an inferior wall infarction could not be excluded. There were no significant changes in several subsequent electrocardiograms taken prior to transplantation, the abnormal S-T segments and T waves remaining stable. A cube vector representation of QRS depolarization (Fig. 9) showed significant displacement of the initial forces anteriorly, inferiorly and somewhat to the right. There was complete absence of the normal anterior left-sided forces, and the main body of the loop was displaced superiorly and posteriorly.

The chest roentgenogram revealed enlargement of all chambers with prominent pulmonary vasculature and pleural effusion at the right base.

Laboratory findings were hematocrit 37 per cent, white blood cell count 11,300 per cu. mm., urine protein 1+ with no sugar or acetone, blood urea nitrogen 30 mg. per cent, creatinine 1.5 mg. per cent, sodium 139 mEq./L. potassium 4.5 mEq./L., chloride 81 mEq./L., carbon dioxide combining power 35.5 mEq./L., fasting blood sugar 122 mg. per cent and prothrombin time 27 sec. (control 12 sec.). The blood type was AB, Rh positive.

Right and left heart catheterization demonstrated moderate pulmonary hypertension (mean 30 mm. Hg), elevated pulmonary wedge pressure (a = 20, v = 27 mm. Hg), and left ventricular end-diastolic pressure (20 mm. Hg) rising to 28 mm. Hg after cineangiography. The left ventricular angiogram demonstrated poor contractility of the myocardium but no aneurysmal dilatation. There was no evidence of valvar disease. Cardiac output, determined by the dye-dilution method, was 4.8 L./min.

From these studies we concluded that the patient had severe coronary artery disease with previous myocardial infarctions, severe ventricular myocardial failure and moderate pulmonary hypertension. He remained dyspneic at complete bed rest, with severe heart failure in spite of continued efforts to improve his cardiac status.

The Donor: On January 9, 1968, a 29 year old

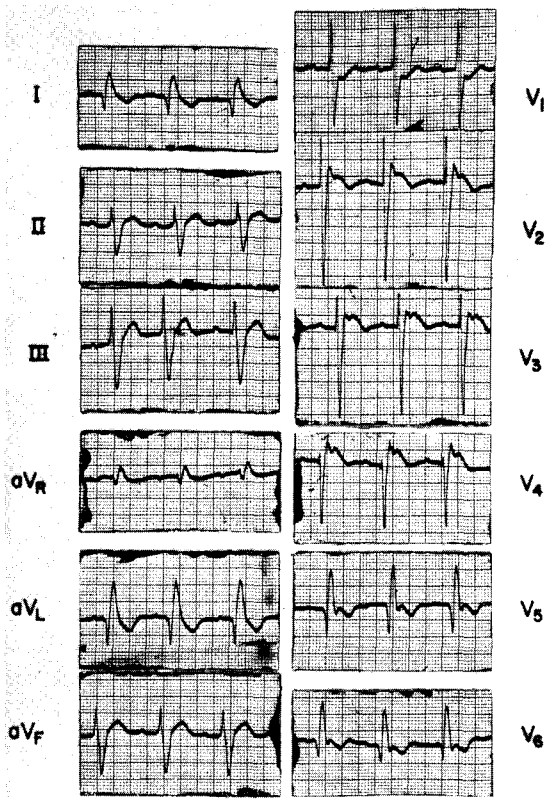

Figure 8. Case 2. *Electrocardiogram.*

woman was transferred from New Jersey to the Maimonides Medical Center after a massive intracerebral catastrophe. She had been comatose for 19 hours before transfer and for the previous 9 hours had required assisted ventilation. Cardiac arrest had occurred at the time of respiratory arrest and was of unknown duration but had responded to sternal compression.

On admission the prospective donor was areflexic, both pupils were dilated and fixed and an electroencephalogram disclosed no cerebral cortical activity. The electrocardiogram disclosed nonspecific S-T changes. Her blood type was AB, Rh positive, the same as that of the proposed recipient. The diagnosis was massive intracranial hemorrhage possibly secondary to a tumor with herniation through the foramen magnum.

Operative Procedure: When the donor's blood pressure began to fall in spite of increasing doses of vasopressors, both donor and recipient were taken to separate operating rooms, and the donor was heparinized (3.5 mg./kg.). At 1:00 P.M. the donor's cardiac activity ceased. Cardiectomy was performed through a midline sternotomy as described in the first case, excising as much of the posterior atrial walls as possible and leaving long aortic and pulmonary cuffs. A vascular clamp was placed across the ascending aorta and a catheter was placed in the root of the aorta through a purse-string suture. At 1:15 P.M. perfusion of this donor heart was begun with homologous blood in glucose and buffered electrolyte solution at a temperature of 28° C. (Fig. 10). Pressure and flow at this time were 20 mm. Hg and 20 ml./min., respectively. These were increased to a maximum of 60 mm. Hg and 45 ml./min. while the temperature of the perfusate rose to 30° C. Mean flow was 42.9 ml./min. at a mean pressure of 48.7 mm. Hg for 36 min.

The recipient had been prepared simultaneously. Now a median sternotomy and right femoral artery cutdown procedure were performed. Occluding tapes were placed about the venae cavae, which were cannulated through the right atrium. The femoral artery was cannulated, and extracorporeal circulation was instituted with the use of a rotating disc oxygenator with hemodilution of homologous blood with glucose and water. Total body hypothermia to 30° C. was instituted at the time of extracorporeal circulation.

A large vascular clamp was placed through the transverse sinus as far distal as possible, and the recipient's diseased heart was resected, leaving generous margins of the posterior atrial walls and long aortic and pulmonic stumps. The donor's heart was then implanted. Because the donor atria were considerably smaller than those of the recipient, it was necessary to form the atria of the donor heart into

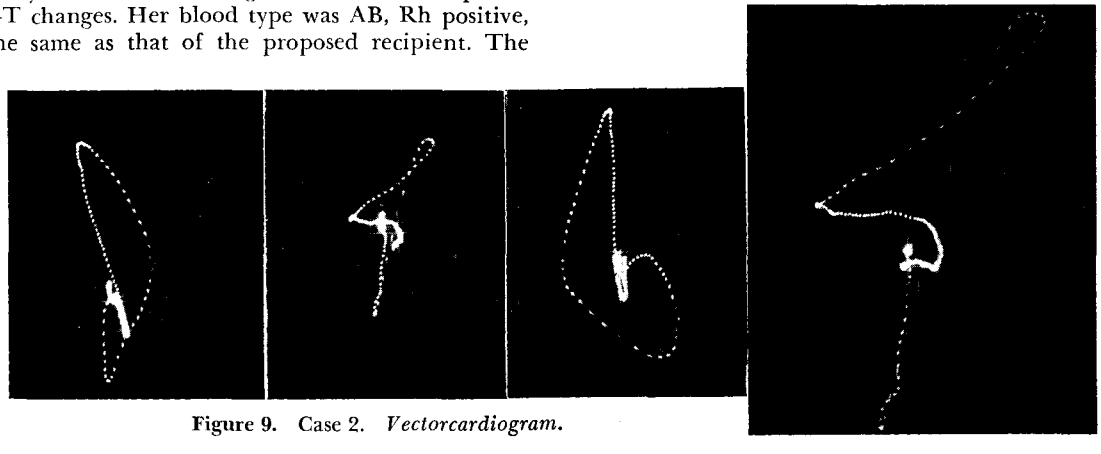

Figure 9. Case 2. *Vectorcardiogram.*

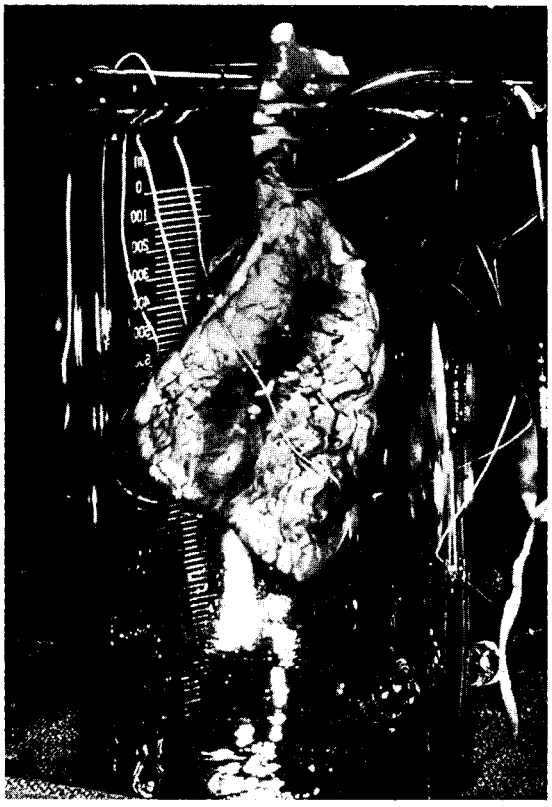

Figure 10. Case 2. *Isolated perfusion of donor organ.*

larger chambers by connecting incisions through the pulmonary veins on the left and the venae cavae on the right. The left atrium was sutured first with a continuous over and over suture of No. 1 silk. The left and right portions of the septum were sutured continuously with the respective atria in similar manner. After completion of the right atrial anastomosis, the aorta was anastomosed with the use of a continuous everting mattress suture of 4-0 Tevdek re-enforced with an over-and-over layer of 3-0 silk. Coronary perfusion continued during the anastomosis. At its conclusion the coronary perfusion catheter was removed, air flushed from the root of the aorta, and the coronary arteries were perfused by the main pump. The pulmonic anastomosis was made in a similar fashion to the aortic. Air was then flushed from both sides of the heart with buffered electrolyte solution instilled through previously placed catheters. Considerable discrepancy in the size of the recipient's pulmonary artery and aorta compared to the donor's was corrected by fashioning the aortic arch and pulmonary artery bifurcation of the donor heart to fit the ascending aorta and pulmonary artery of the recipient.

Because of tachyarrhythmias and manifestations of heart failure each time the bypass flow was reduced, the patient was slowly weaned from the heart-lung machine. For a period of about 15 minutes the heart was able to maintain adequate arterial pressures (Fig. 11). Because of recurrent failure, the decision was then made to insert an intra-aortic phase-shift balloon pump for support of the heart.[8] Wire electrodes were implanted in the left ventricular myocardium to provide a direct epicardial electrocardiogram and a source for pacing should this become necessary. The sternal incision was then closed. Both pleural spaces were drained and the patient left the operating room for a special sterile recovery area which had been provided. In spite of continuous intraaortic phase-shift pumping, cardiac failure persisted and the patient died $10^1/_2$ hours after the operation.

Postmortem examination of the recipient's excised heart (Fig. 12) showed the left ventricle to be a thin-walled, fibrous sac. The ventricles weighed 550 gm. There was no valve disease, and the coronary arteries were narrowed diffusely.

The donor's heart weighed approximately 250 gm. It contained multiple areas of subepicardial hematoma of recent origin. Suture lines were intact, and there were no signs of leakage and no intracardiac thrombi.

The examination of the donor's brain confirmed the presence of massive intracranial hemorrhage into a posterior fossa tumor with herniation through the foramen magnum.

Discussion

The problems attendant upon translating successful experimental experiences into clinical practice were reviewed in the spring of 1966 and classified as follows: (1) selection of the recipient, (2) selection of the donor, (3) surgical technic and (4) postoperative management.

Selection of the Recipient

The criteria for selection of a potential recipient required that the patient's life span be severely limited and that no other form of therapy be of benefit. Cardiac catheterization with angiocardiography was considered a prerequisite. In addition, no recipient was to be selected who had evidence of other severe systemic disease that might jeopardize survival.

The first potential candidate died of complex congenital anomalies at 10 weeks of age, when a suitable donor could not be found. The infant in whom transplantation was performed had required a palliative shunt for what was believed to be tricuspid atresia but was actually a severe Ebstein's malformation in which the attachments of the leaflets and chordae of the tricuspid valve created a nearly

total obstruction to right ventricular outflow. The adult patient (Case 2) was dyspneic at rest as a result of severe myocardial damage from diffuse coronary artery disease.

SELECTION OF THE DONOR

The requirements to be met in the selection of potential donors were the following: (1) freedom from transmissible disease; (2) histocompatibility with the prospective recipient, as reflected by compatibility of the major blood groups and, if possible, by tissue typing (although the evidence for the latter was, in the spring of 1966, inconclusive); and (3) assessment of the donor organ and diagnosis of death by a cardiologist or pediatrician and an anesthesiologist.

Anencephalic newborns were a reasonable choice as donors for babies. The most suitable adult donors seemed to be patients who had been well until sudden intracerebral catastrophe. No patient was to be considered a potential donor until it was evident that death was imminent in spite of the best possible medical care. This meant that the electroencephalogram would be flat and that all reflexes including spontaneous ventilation would be absent. At the time the patient demonstrated cardiovascular instability, as manifested by an irregular electrocardiogram or falling blood pressure for which vasopressors were required, he would be moved to an operating room to have myocardial viability maintained by the anesthesiologist until the recipient could be readied.

Since these criteria were applied in each of the cases in which transplantation was considered, all 3 donors were subjected to periods of hypoxia. The hypothermia of the infants undoubtedly preserved myocardial viability during this time, whereas in the adult, hypothermia did not occur prior to cardiac arrest. If clinical death is recognized as occurring with the absence of any central nervous system activity and with failure of the cardiovascular and respiratory systems, undue prolongation of the agonal state, which subjects the heart to hypoxia and acidosis, may be avoided.

SURGICAL TECHNIC

The surgical methods had been refined in over 300 experiments on adult dogs and puppies.[1-6] The method of excising the heart preserved the posterior atrial walls and the sinoauricular node as originally suggested by Lower and Shumway.[9,10] The procedure was carried out in adult dogs with standard clinical extracorporeal circulation technics. Cardiopulmonary bypass in infants, however, poses numerous problems, and so the alternative of hypothermia with circulatory arrest, used in experiments on puppies, was adopted.

Bilateral anterior thoracotomy was performed in the infant. It should be possible to perform transplantation in infants through a midline sternotomy, thereby avoiding the need to enter both pleural spaces and lessening the risk of pulmonary and pleural complications.

The cannulation of the cavae in the adult patient posteriorly in the right atrium near the atriocaval junctions did not interfere with the procedure. Substantial differences in the size of donor and recipient hearts and great vessels were overcome by a combination of tailoring methods.

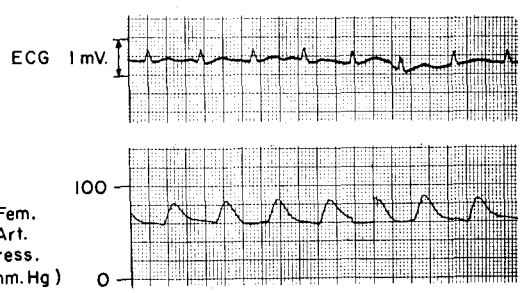

Figure 11. Case 2. *Electrocardiogram and femoral arterial pressure* after implantation of graft.

Figure 12. Case 2. *Recipient's excised heart.*

POSTOPERATIVE MANAGEMENT

The major postoperative problem following immediate survival was expected to be homograft rejection. Animal studies had demonstrated that the magnitude of the R wave and sinoatrial rhythm disturbances indicated rejection in dogs and that this usually could effectively be combatted by Imuran® and hydrocortisone. Both infant and adult recipients received hydrocortisone preoperatively. It was appreciated that the immune response might be difficult to detect postoperatively, and electrodes were therefore sutured to the epicardium to provide direct myocardial leads for electrocardiographic recording and pacing.

Although metabolic and respiratory acidosis were regularly corrected in puppies, the infant died in severe acidosis. It is possible that the metabolic component was not entirely the result of hypothermia, but rather, at least in part, of poor cardiac output. Effectiveness of myocardial contractility in infants remains a very difficult parameter to assess, and direct measurements are not possible.

The cause of death in the second case also appeared related to poor cardiac output. This may be assumed to be related to damage sustained by the donor heart. The donor had experienced one and possibly two episodes of cardiac arrest with hypoxia in which sternal compression and vasopressors were needed to effect resuscitation. Although her heart resumed normal contractility and appeared able to sustain her blood pressure at normal levels, it may be that it had sustained prior hypoxic injury as well as traumatic damage from the sternal compression. Perfusion of this heart under moderate hypothermia may have been inadequate, in view of the prior injury.

SUMMARY

Experience with human heart transplantation is reported. A technically successful infant heart transplantation was performed on December 6, 1967. The child died 6½ hours postoperatively in severe metabolic and respiratory acidosis.

Another heart transplantation was performed on January 5, 1968; the recipient was a 57-year old man. The donor heart was unable to support the circulation, and the patient died $10^1/_2$ hours postoperatively.

Problems in the selection of donors and of recipients, in the surgical technic, and in the postoperative management are discussed.

ACKNOWLEDGMENT

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